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BRIEF COMMUNICATION

Periodic vertigo and downbeat nystagmus while supine: Dysfunction of Purkinje cells coding gravity

Byeongcheon Lee[1], Min-Ku Kim[1], So-Yeon Yun[1], Eek-Sung Lee[2], Hyo-Jung Kim[3], Jeong-Yoon Choi[1,4] & Ji-Soo Kim[1,4]

[1]Dizziness Center, Clinical Neuroscience Center, and Department of Neurology, Seoul National University Bundang Hospital, Seongnam, South Korea
[2]Department of Neurology, Soonchunhyang University College of Medicine, Bucheon, South Korea
[3]Research Administration Team, Seoul National University Bundang Hospital, Seongnam, South Korea
[4]Department of Neurology, Seoul National University College of Medicine, Seoul, South Korea

Correspondence
Jeong-Yoon Choi, Department of Neurology, Seoul National University College of Medicine, Seoul National University Bundang Hospital, 173-82 Gumi-ro, Bundang-gu, Seongnam-si 13620, Gyeonggi-do, South Korea. Tel: 82 31 787 7469; Fax: 82 31 719 6828; E-mail: saideiju@gmail.com

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Abstract

Cerebellar nodulus and uvula and their connections with the vestibular nuclei form the so-called velocity-storage circuit. Lesions involving the velocity-storage circuit give rise to positional vertigo and nystagmus. Herein, we present a 32-year-old man with cerebellar nodulus and uvular hemorrhage who showed periodic vertigo and downbeat nystagmus in the supine position. To explain this unusual pattern, we adopted velocity-storage model with a lesion on the neural connection between the gravity and inertia estimators, resulting in periodic neural impulses and a gravity bias in a specific position. This report expands the spectrum of central positional nystagmus due to dysfunction of the velocity-storage mechanism.

Introduction

The velocity-storage circuit is critical for estimating head motion and position by computing rotational velocity, gravity orientation, and inertial acceleration.[1] Lesions involving this circuit can cause positional vertigo and nystagmus,[2] either transient but intense (referred to as the paroxysmal form)[3] or long-lasting but mild (known as the persistent form).[4]

Herein, we describe a patient with cerebellar hemorrhage exhibiting a novel type of central positional vertigo and nystagmus characterized by periodic occurrences exclusively in the supine position. By analyzing patient's clinical features based on the model of the velocity-storage circuit, we aim to discover the mechanism behind this brand new phenomenon.

Patient and Methods

Case report

A 32-year-old man presented with 7-year vertigo after cerebellar hemorrhage in the nodulus and uvula (Fig. 1A). The hemorrhage caused severe spontaneous vertigo for a few days. He then experienced paroxysms of vertigo when extending his head or lying down. Furthermore, in the supine position, he experienced a recurring sensation of his head being pulled downward for about 15 s nearly every minute, preventing him to sleep in the supine position for years.

Neurological examination showed no spontaneous, gaze-evoked, head-shaking, or vibration-induced nystagmus. Smooth pursuit and saccades were normal. The patient reported intense vertigo and paroxysmal downbeat nystagmus lasting about 20 s when lying down. Transient upbeat nystagmus was observed on sitting up from a supine position. During supine, the patient developed periodic vertigo and downbeat nystagmus with an initial peak and a gradual decrease over 10–15 s. This pattern of paroxysmal vertigo and nystagmus repeated nearly every minute during a 10-min observation (Fig. 1B; Video S1). He also showed persistent apogeotropic nystagmus when turning his head to either side while supine (i.e., right beating nystagmus in the left ear-down position and vice versa). Vestibular functions in the head impulse, bithermal caloric, vestibular-evoked myogenic potentials, and

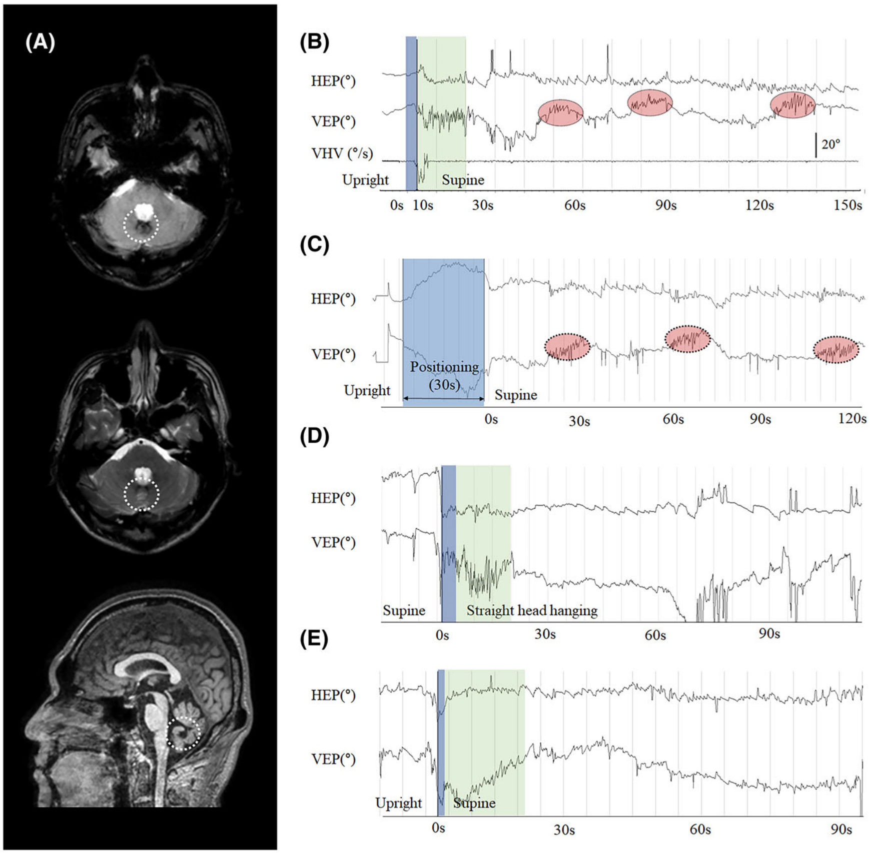

Figure 1. Magnetic resonance imaging (MRI) and recording of nystagmus modulation. (A) Gradient echo and T2-weighted MRI show a low signal intensity involving the cerebellar nodulus and uvula, and T1-weighted sagittal MRI shows tissue loss in the corresponding area, suggestive of old hemorrhage. (B) Rapid positional change (blue column) from upright to supine evoked strong downbeat nystagmus just after positioning (green column), followed by periodic downbeat nystagmus with an interval of about 30 s (red circles). (C) Positioning from upright to supine with a slow velocity (duration at 30 s, blue column) did not induce paroxysmal downbeat nystagmus just after positioning, but it was followed by periodic downbeat nystagmus (red circles). (D) Straight-head hanging (blue column) evoked vigorous paroxysmal downbeat nystagmus just after positioning (green column), but without following periodic downbeat nystagmus. (E) Administration of phenytoin (200 mg per day) did not affect the paroxysmal downbeat nystagmus just after positioning, but abolished the following periodic downbeat nystagmus while supine. Blue and green columns and red circles in each figure indicate positioning, paroxysmal downbeat nystagmus just after positioning, and periodic downbeat nystagmus, respectively.

rotation chair tests were normal. The paroxysmal vertigo and nystagmus did not respond to 4-aminopyridine, baclofen, or clonazepam.

Hypothesis and evaluation

To explain the patient's periodic vertigo and downbeat nystagmus, we considered two possibilities: cerebellar adaptation akin to periodic alternating nystagmus and periodic neuronal discharges in the nodulus and uvula, as in the paroxysmal ocular tilt reaction.[5,6] A preceding velocity bias is needed for cerebellar adaptation, not for periodic neuronal discharge, and the preceding velocity bias for this patient would have been paroxysmal vertigo and downbeat nystagmus on position changes. Therefore, we evaluated the modulation pattern of positional nystagmus based on the following considerations. First, to verify that the development of paroxysmal vertigo and nystagmus depended on positioning velocity,[7] we adopted two different positioning speeds: Slow and fast, with approximate durations of 15 and 2 s for lying down, respectively. Second, if cerebellar adaptation was the underlying mechanism, we expected other types of periodic vertigo and nystagmus would occur in other head positions, as the patient also showed paroxysmal upbeat nystagmus when resuming the sitting position after lying down and apogeotropic nystagmus during the supine head roll test. Lastly, we investigated the effect of phenytoin since the patient would benefit from antiepileptic drugs if periodic neuronal discharges were the mechanism.

Experiments followed the Declaration of Helsinki. Institutional review board approval (B-2208-772-703) and patient consent were obtained.

Results

The effects of positioning velocity when lying down

Unlike fast lying down (Fig. 1B), slow positioning did not provoke paroxysmal vertigo and downbeat nystagmus after lying down. However, periodic vertigo and nystagmus developed when the patient was supine, regardless of the positioning velocity of lying down (Fig. 1C).

The effects of different head positions

Even though the intensity of paroxysmal downbeat nystagmus was maximal just after straight-head hanging, subsequent periodic vertigo and nystagmus did not occur while maintaining the head position (Fig. 1D). Likewise, no periodic vertigo and nystagmus were induced during the Dix–Hallpike test in either direction or during the supine head-roll test.

The effect of phenytoin

After taking 200 mg of phenytoin daily for 2 weeks and 400 mg thereafter, the patient reported resolution of periodic vertigo in the supine position. The examination also confirmed the disappearance of periodic vertigo and downbeat nystagmus while supine, even though paroxysmal vertigo and downbeat nystagmus still presented just after the patient moved into the supine position (Fig. 1E). Furthermore, periodic vertigo and nystagmus emerged again after the discontinuation of phenytoin.

Discussion

We considered two mechanisms to account for periodic vertigo and nystagmus in the supine position: cerebellar adaptation and periodic neuronal discharges. The former would compensate for a velocity bias,[5] and the latter would involve abnormal hyperactivity.[6] However, the lack of a relationship between the preceding velocity bias and the development of periodic vertigo and nystagmus contradicts the role of cerebellar adaptation. Furthermore, the duration and interval of periodic vertigo and nystagmus are too short for the cerebellar adaptation to occur because periodic alternating nystagmus, in which cerebellar adaptation is involved, changes direction every 2 min.[5] Medications such as baclofen and clonazepam, potentially effective in periodic alternating nystagmus,[8,9] were ineffective in our patient. Hence, we favored periodic neuronal discharges as the mechanism, and the suppression of vertigo and nystagmus with phenytoin administration further supported this idea.

The otolithic organs detect gravitoinertial acceleration (GIA) as the summation of two indistinguishable physical factors: gravitational (G) and inertial (I) accelerations. The nodulus and uvula form the velocity-storage circuit which allows GIA to be differentiated into gravitational and inertial accelerations by estimating the gravity direction using an extra-otolith cue (known as the canal signal) and then subtracting it from GIA to estimate inertia ($I = GIA - G$).[10] Indeed, recording of the neuronal activities in the nodulus and uvula showed the neurons encoding the gravity (tilt-coding cells) and inertia (translation-coding cells) selectively or as their sum (GIA-coding cells).[11] Moreover, those neurons have a directional preference for activation in head-centered coordination.[11,12]

These findings suggest that if a nodulouvular lesion partially damages and periodically excites neurons with a specific directional preference, irrespective of their representation (G or I), subsequent neural computations would be inaccurate. In our patient, periodic vertigo and nystagmus did not develop in the Dix–Hallpike, ear-down, or straight-head hanging positions. Originally, we tested different head positions to study the effect of cerebellar adaptation. However, the observation of periodic vertigo and nystagmus exclusively in the supine position might imply damage to neurons with a directional preference for nasooccipital direction in head-centered coordination. Moreover, the lesions in our patient are likely related to the damage of tilt-coding cells rather than the translation-coding cells, as the former cells create false inertia exclusively in the supine position, while the latter cells create false inertia in the nasooccipital direction regardless of head position.

Modeling of periodic nystagmus in the supine position

We tested our hypothesis by simulating a velocity-storage model introduced elsewhere.[1,13–15] We postulated that a lesion would impair the connections between the tilt-coding and translation-coding cells. The lesion possessed two specific characteristics: positional specificity and periodicity. We applied periodic neural impulses (with a peak amplitude of $0.3 \times$ gravitation toward the occiput) when the gravitational direction was toward the occiput. However, this manipulation generated no vertical nystagmus. Therefore, we added a directional bias to the tilt-coding cells so that the periodic neural impulses could bias the estimated gravitational direction caudally. This bias can

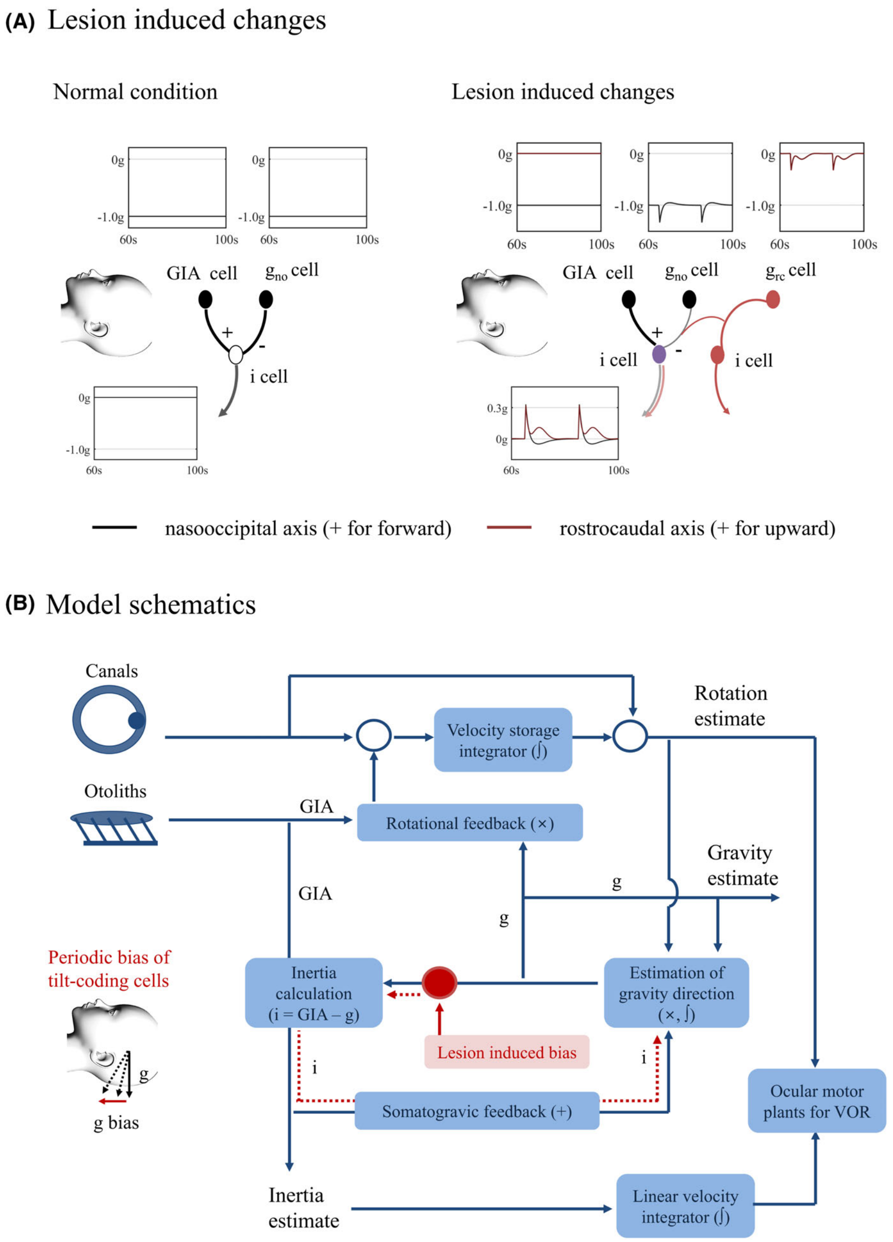

Figure 2. The modeling for periodic vertigo and downbeat nystagmus while supine. (A) Lesion-induced changes in the neural connections among the neurons coding gravitoinertial acceleration, gravitation acceleration, and inertia. A right-hand coordinate system is adopted for the model. Positive values indicate forward, left, and upward. (B) Schematics of the velocity-storage model with a lesion involving the nodulus and uvula. Note that the lesion (red circle) is located at the connection between gravity estimation and inertial calculation, while leaving the gravity information to return to gravity estimation and rotational feedback intact. The lesion would cause errors in inertia estimation and gravity estimation through the effect of the somatogravic feedback (red dotted line). Detailed explanations of the model schematics are presented in the text. g = gravitational acceleration, g_{no} and g_{rc} cells = tilt-coding cells with a preference for nasooccipital and rostrocaudal direction each, GIA = gravitoinertial acceleration, GIA cell = cerebellar vermis neuron representing GIA. i = inertial acceleration, and i cell = inertia coding cerebellar vermis neuron.

develop when an aberrant neuronal connection is formed between the tilt-coding cells, which are preferentially activated when gravity is aligned along the nasooccipital axis and the cells that are activated along the rostrocaudal axis during the regeneration process after the cerebellar hemorrhage involving the nodulus and uvula (Fig. 2).

This model simulation successfully reproduced the observed periodic downbeat nystagmus in our patient

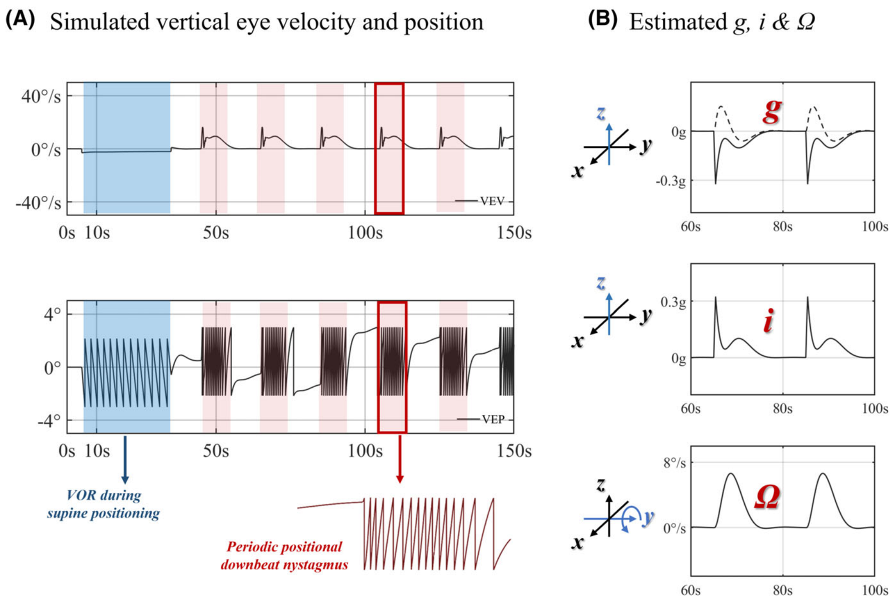

Figure 3. Results of the model simulation. (A) The upper panel shows the vertical eye velocity (after removing saccades), and the lower panel exhibits the vertical eye position (the positive values denote an upward direction). (B) Estimated gravity (g), inertia (i), and rotational (Ω) cues in the model. Due to the lesion involving the cerebellar nodulus and uvula, gravity (the upper panel) is periodically directed caudally (solid line), which causes an erroneous estimation of the inertia (the middle panel). This also leads to a further error in gravity estimation by the somatogravic feedback loop (the dotted line in the upper panel). The incorrect estimation of gravity activates the rotational feedback loop and causes a downward rotational cue in the pitch axis (the lower panel). A right-hand coordinate system is adopted for the model. Positive values indicate forward, leftward, and upward for linear acceleration and leftward, downward, and clockwise for rotation, while x, y, and z indicate the naso-occipital, interaural, and rostrocaudal axes, respectively.

(Fig. 3A). The output showed that the estimated gravity relayed to the translation-coding cells was in the caudal direction (solid line), while that relayed to other regions, such as the rotational feedback loop, was in the rostral direction (Fig. 3B, upper panel). The estimated inertia (GIA—gravity), therefore, oscillated rostrally (Fig. 3B, middle panel), which would have acted as an initial drive for downbeat nystagmus (inertia in the rostral direction indicates translation directed caudally). The rotational feedback driven by the discrepancy between GIA and estimated gravity generated a downward rotational cue (Fig. 3B, lower panel), an additional source for the nystagmus.

In conclusion, this report presents a novel pattern of positional vertigo and nystagmus—periodic vertigo and downbeat nystagmus in the supine position—as a complication of cerebellar hemorrhage affecting the nodulus and uvula. The explanation is based on periodic neuronal discharges and impaired neural connections between the gravity and inertia estimators within the velocity storage circuit, attributing the observed phenomenon mainly to the translational VOR component. However, our experiments could not definitively establish the source of periodic vertigo and nystagmus. Additionally, there may be other lesion locations, such as tilt-coding cells per se or GIA-coding cells, contributing to the phenomenon. Therefore, further clinical and experimental evidence is needed. Overall, this report can broaden our understanding of central positional vertigo and nystagmus resulting from lesions in the vestibulocerebellum, responsible for estimating gravity orientation, rotational velocity, and linear acceleration.

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Author Contributions

Byeongcheon Lee interpreted the data and wrote the article. Min-Ku Kim, So-Yeon Yun, and Eek-Sung Lee performed experiments and analyzed the data. Jeong-Yoon Choi designed and conceptualized the study, interpreted the data, and wrote the article. Ji-Soo Kim analyzed and interpreted the data and revised the article.

Conflict of Interest

Nothing to report.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Video S1
Video S1 Legend

